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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/601,852	12/19/2000	Petrus J.A. Meeuwsen	251502008400	5307

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EXAMINER	
CHOWDHURY, IQBAL HOSSAIN	
ART UNIT	**PAPER NUMBER**
1652	

DATE MAILED: 07/03/2006

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/601,852	MEEUWSEN ET AL.	
	Examiner	Art Unit	
	Iqbal Chowdhury, Ph.D.	1652	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *07 April 2006*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-3,6,21,22 and 45-49* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-3,6,21,22 and 45-48* is/are rejected.

7)☒ Claim(s) *49* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☒ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☒ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☒ All b)☐ Some * c)☐ None of:

1.☒ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Application Status

In response to a previous Office action, a non-final requirement (mailed on 1/6/2006), Applicants filed a response and amendment received on April 7, 2006. Claims 1-2, and 20-21, are amended and added new claims 45-49. Claims 4-5 and 31-32 are cancelled and claims 12, 35-38, and 43 remained cancelled. Thus, Claims 1-3, 6, 20-21, and 45-49 are pending in the instant Office action and will be examined herein.

Applicants' arguments filed on April 7, 2006, have been fully considered but are deemed to be persuasive to overcome some of the rejections previously applied. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn.

Regarding lack of unity the applicants again argue without evidence stating that because claim 1 is amended, all the claims which are dependent on claim 1 should be rejoined and claiming that lack of unity no more exists. This is not found persuasive because such amendment does not change core point that a polypeptide having 80% identical to SEQ ID NO: 2 having galacturonase activity i.e. which hydrolyze galacturonic acid polymer in plant fruit cell wall in endolytic fashion while galacturonan may or may not be substituted with xylose, is known in the art (see previous office action). Therefore, this polypeptide activity mainly is cleaving galacturonic acid polymer at the internal glycosidic bond. The applicant clearly define the endo-xylogalacturonase activity in the specification p3 lines 11 that "endoxylogacturonase activity is defined as the ability to cleave a galacturonic acid polymer found in pectin which may be at least partially substituted with xylose at internal glycosidic bonds". Furthermore, in p3 lines 23 of the specification, applicants also disclose, "The two galacturonic acid residues between which the

polypeptides of the invention cleave may both be (xylose) substituted or only one may be (xylose) substituted or (preferably) neither may be (xylose) substituted". Therefore, this polypeptide is a galacturonase, which cleaves galacturonic acid-galacturonic acid linkage (p3, lines 16 of the specification) in the pectin. Therefore, this enzyme is nothing but a xylogalacturonase or xylogalacturonan hydrolase or polygalacturonase or polygalacturonic acid hydrolase, galacturonase or galacturonan hydrolase or galactanase, which are almost functionally same as the polypeptide, disclose by the applicant. For the reasons above and as discussed in length in the previous office action, the requirement is maintained.

Priority

Acknowledgement is made of applicants claim for foreign priority of EP 98300952.3 of 2/10/1998.

Maintained-Claim Objections

Previous objection of claim 3 because of the recitation "A ---", which refers to a previous claim. "A ---" should be changed to "The ---", is maintained.

New-Claim Objections

Claim 48 is objected to under 37 CFR 1.75 as being a substantial duplicate of claim 1. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Appropriate correction is required.

Maintained-Claim Rejections - 35 USC § 101

35 U.S.C. 101 reads as follows:

> Whoever invents or discovers any new and useful process, machine, manufacture, or composition of matter, or any new and useful improvement thereof, may obtain a patent therefor, subject to the conditions and requirements of this title.

Previous rejection of Claims 2-3 under 35 U.S.C. 101 because the claimed invention is directed to non-statutory subject matter is maintained.

In the absence of the hand of man, naturally occurring nucleic acids and /or proteins are considered non-statutory subject matter. *Diamond and Chakrabarty*, 206 USPQ 193 (1980). This rejection may be overcome by amending the claims to contain wording such as "An isolated and purified protein". For examination purpose the claim is read as such.

Maintained-Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Previous rejection of Claims 2-3 rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement is maintained. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention. This rejection has been described in length in previous Office Actions. Applicant's amendments and arguments have been fully considered but are not deemed persuasive for the following reasons.

Claim 2, an independent claim, which is directed to a genus of protein molecule encoding any polypeptide having endo-xylogalacturonase or endo-xylogalacturonan hydrolase activity or any endo-xylogalacturonase activity. The specification teaches the structure of only a single

representative species of such proteins. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than the functionality of encoding any polypeptide having endo-xylogalacturonase or endo-xylogalacturonan hydrolase activity or any endo-xylogalacturonase activity. Applicants argue that claim 1 is amended which includes structural features of a substantial portion of the genus of endo-xylogalacturonase. Therefore, claim 1 and all the dependent claims have appropriate written description and the applicants further submit that a skilled artisan would understand that the applicants had possession of the genus of polypeptides defined in claim 1.

This is not found persuasive because claim 2 is an independent claim and the limitation added to claim 1 will not apply to claim 2 and its dependent claim 3. Therefore, the rejection is maintained as described in the previous office action.

Previous rejection of claims 1-3 and 21-22 under 35 U.S.C. § 112, first paragraph, as failing to comply with enablement requirement, is maintained and newly adding claims 45-48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with enablement requirement based on the arguments presented by the examiner in the previous office action. This rejection has been described in length in previous Office Actions. Applicant's amendments i.e. "at least 80% identical to SEQ ID NO: 2" and arguments have been fully considered but are not deemed persuasive for the following reasons.

As mentioned in the previous office action, Claims 1 and 21-22 and newly added claims 45-48 are so broad as to as to encompass any polypeptide having endo-xylogalacturonase or endo-xylogalacturonan hydrolase activity or any xylogalacturonase having 80% identity to an enzyme of SEQ ID NO: 2 and compositions thereof. Claim 2 recites that any polypeptide having

endo-xylogalacturonase activity, which is obtainable from any fungus, and is capable of cleaving xylogalacturonan between adjacent galacturonan non-terminal units and Claim 3 recites that the said fungus is of the genus Aspergillus. The scope of the claims is not commensurate with the enablement provided by the disclosure with regard to the extremely large number of polypeptides broadly encompassed by the claims. The scope of the claimed invention is very broad in the context of 80% identity to SEQ ID NO: 2. How many polypeptides having xylogalacturonase activity can be encompassed by these claims?

Applicants argue that the present application describes which changes can be tolerated in a protein amino acid sequence to obtain the desired activity and applicants also submit that the present application describes on page 22-23 assays for identifying and confirming endo-xylogalacturonase activity, and furthermore, example 3.3 shows how a skilled artisan can determine whether a polypeptide has endo-xylogalacturonase activity. Applicants further argue that polypeptides of claim 1 are defined as either SEQ ID NO: 2, sequences highly homologous thereto or large fragments thereof, a skilled artisan would understand how to make such sequence and test them for endo-xylogalacturonase activity without undue burden.

While as discussed by applicants the specification provides some guidance with regard to which amino acids of the enzyme can be modified, the guidance provided is much too general in nature to enable the full scope of the rejected claims. Applicants argue that polypeptides of claim 1 sequences are highly homologous thereto, which is not persuasive because highly homologous or 80% identical means 20% non-identical sequences encompassed by the claims. It is noted that 80% identities to SEQ ID NO: 2 (406 amino acid residues) as recited in the claims encompasses enzymes having 81 amino acids altered.

While methods to produce a polypeptide or its variants of a known sequence such as site-specific mutagenesis, random mutagenesis, etc. are well known to the skilled artisan producing variants as claimed by applicants (i.e., encoding a endo-xylogalacturonase capable of cleaving xylogalacturonan between adjacent galacturonan non-terminal units requires that one of ordinary skill in the art know or be provided with guidance for the selection of which of the infinite number of variants have the claimed property. With only the limited guidance provided by the specification one of ordinary skill would be reduced to the necessity of producing and testing virtually all of the possibilities. This would clearly constitute **undue** experimentation. Guo et al. teach that the percentage of random single substitution mutations which inactivate a protein for the protein 3-methyladenine DNA glycosylase is 34% and that this number appears to be consistent with other studies in other proteins as well. Guo et al. further show in Table 1 that the percentage of active mutants for multiple mutants appears to be exponentially related to this by the simple formula $(.66)^x$ X 100% where x is the number of mutations introduced. Applying this estimate to the instant protein 80% identity allows up to 81 mutations within the 406 amino acids of SEQ ID NO: 2 and thus only $(.66)^{81}$ X 100% or 2.4 x 10^{-13}% of random mutants having 80% identity would be active. Similarly, at 95% identity 2.4 x 10^{-2}% would be active. Current techniques (i.e., high throughput mutagenesis and screening techniques) in the art would allow for finding a few active mutants within several hundred thousand inactive mutants as is the case for the claims limited to 95% identity (despite even this being an enormous quantity of experimentation that would take a very long time to accomplish) but finding a few mutants within several billion or more as in the claims to 80% or less identity would not be possible. While enablement is not precluded by the necessity for routine screening, if a large amount of

screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed. Such guidance has **not** been provided in the instant specification.

While enablement is not precluded by the necessity for routine screening, if a large amount of screening is required, the specification must provide a reasonable amount of guidance with respect to the direction in which the experimentation should proceed.

For all the reasons above, the examiner finds that amendment of claim 1 does not describe the structural features of claimed genus in sufficient detail to overcome the rejection. Therefore, for the reasons above, the rejection is maintained.

New-Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1, 20, 21, and 45-48 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter, which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

These claims are directed to use of a genus of protein molecule having 80% identical to SEQ ID NO: 2 or a fragment of either sequence, which is at least 200 amino acids long. The specification teaches the structure and function of only a single representative species of such proteins and does not contain any disclosure of the structure and function of all protein that are

80% identical to SEQ ID NO: 2 or all the fragments which are at least 200 amino acid long. Moreover, the specification fails to describe any other representative species by any identifying characteristics or properties other than reciting that a fragment of SEQ ID NO: 2, which is 200 amino acids long. The genus of protein, having 80% identity to SEQ ID NO: 2 is a large variable genus with the potentiality of encoding many different proteins and a fragment of SEQ ID NO: 2 having at least 200 amino acids long, the specification fails to teach all such proteins or fragments those are functionally similar to SEQ ID NO: 2. Therefore, many structurally and functionally unrelated polypeptides are encompassed within the scope of these claims. Given this lack of description of representative species and functions encompassed by the claims, the specification fails to sufficiently describe the claimed invention in such full, clear, concise, and exact terms that a skilled artisan would recognize that applicants were in possession of the claimed invention.

Maintained-Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

A person shall be entitled to a patent unless -

(b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Previous rejection of Claims 2-3 under 35 U.S.C. 102(b) as being anticipated by Renard et al. ("The xylose rich pectins from pea hulls", Int J Biol Macromol. 1997 Aug; 21(1-2): 155-62, see IDS) and Schols et al. (Different populations of pectic hairy regions occur in apple cell walls", Carbohydr Res. 1995 Oct 2; 275(2): 343-60.) is maintained. Applicants argue that

because claims 4 and 5 were not included in this art rejection and subject matter thereof has been included in claim 1, therefore, the rejection should be withdrawn. Applicants further submit that these references do not disclose an endo-xylogalacturonase and the present invention is directed to endo-xylogalacturonase which degrade xylogalacturonan of subunit 1 of the "hairy" region of the pectin. Applicants further argue that Renard et al. describes fractions hydrolyzed by endo-polygalacturonase, which were not hydrolyzed by xylanases and both these enzymes differ from the endo-xylogalacturonase as claimed. Endo-xylanase is an enzyme able to hydrolyze xylan polymer in an endo fashion, and endo-polygalacturonase is an enzyme, which degrades a smooth, homogalacturonan regions. This document does not teach or suggest enzymes with polygalacturonase activity. Further, Schols merely teaches isolation of xylogalacturonan subunits present in the "hairy" regions of pectin but it does not teach the hydrolysis thereof, and polygalacturonase and rhamnogalacturonase enzymes are mentioned but differ from the endo-xylogalacturonase as claimed.

Applicant's arguments have been considered but deemed persuasive to over come the rejection. As discussed previously, Renard et al. clearly teach endo-polygalacturonase (Abstract, page 155, line 6; Experimental/Material, page 156 line 8; and Result, page 162, line 5; and Fig. 3, panel (a) and (d). Schols et al. also teach endo-polygalacturionase (PG) (Abstract, page 343, line 5, page 344, line 6 and Table 2). The claimed endo-xylogalacturonase, which hydrolyze galacturonic acid polymer in plant fruit cell wall in endolytic fashion while galacturonan may or may not be substituted with xylose. Therefore, this polypeptide activity mainly is cleaving galacturonic acid polymer at the internal glycosidic bond and applicants clearly define the endo-xylogalacturonase activity in the specification p3 lines 11 that "endoxylogacturonase activity is

defined as the ability to cleave a galacturonic acid polymer found in pectin which may be at least partially substituted with xylose at internal glycosidic bonds". Furthermore, in p3 lines 23 of the specification, applicants also disclose, "The two galacturonic acid residues between which the polypeptides of the invention cleave may both be (xylose) substituted or only one may be (xylose) substituted or (preferably) neither may be (xylose) substituted". Thus, this enzyme is nothing but a xylogalacturonase or xylogalacturonan hydrolase or polygalacturonase or polygalacturonic acid hydrolase, which are functionally same as the polypeptide, disclose by the applicant. Therefore, the polygalacturonase activity of the prior art is encompassed by the xylogalacturonase activity as claimed. Therefore, the rejection is also maintained as discussed.

Summary of Pending Issues

The following is a summary of the issues pending in the instant application:

Claims 1-3, 6, 21-22 and 45-48 stand rejected under 35 U.S.C. § 112 first and 102(b).

Claim 49 objected to as depends on rejected claim.

Conclusion

Claims 1-3, 6, 21-22 and 45-48 are rejected and claim 49 is objected to as depends on rejected claim. Applicants must respond to the objections/rejections in each of the numbered sections in this Office action to be fully responsive in prosecution. **THIS ACTION IS MADE FINAL**. See M.P.E.P. § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO

MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 C.F.R. § 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Iqbal Chowdhury, Ph.D. whose telephone number is 571-272-8137. The examiner can normally be reached on 9:00-5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Ponnathapu Achutamurthy can be reached on 703-272-0928. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

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